Microembolus Detection in Patients With Takayasu’s Arteritis

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Background and Purpose—Takayasu’s arteritis (TA) is a chronic inflammatory disease of unknown etiology that can affect the aorta and its branches. A triphasic pattern of progression of the disease has been described. The inflammatory period, phase I, is characterized by nonspecific complaints, such as fever, arthralgia, and weight loss. Phase II is dominated by vessel pain and tenderness due to vessel inflammation. The final phase, phase III, is the burnt-out or fibrotic stage, in which bruits and ischemia predominate in multiple organs. Neurological symptoms in TA may develop in phases II and III, depending on the extent of involvement of the 4 cerebral branches of the aortic arch. Transient ischemic attacks or stroke may occur in TA because of either the occlusion or embolic material originating from the inflammatory region of the vessel. Therefore, we performed transcranial Doppler (TCD) ultrasonography in patients with TA to detect the presence of microembolic signals (MES). The occurrence of MES may be considered to be a risk factor for the development of stroke. The presence of MES in patients with TA may support the possible contribution of microembolus in the pathogenesis of ischemic stroke. Therefore, in the present study, we investigated the frequency of MES and their relationship with the presence of cerebral ischemic events.

Subjects and Methods

Eighteen patients with TA who had been admitted to Neurology and Rheumatology inpatient departments were enrolled in the present study. The diagnosis of the TA was assessed according to the American College of Rheumatology Criteria for the Classification of Takayasu Arteritis. The presence of ≥3 of the 6 following criteria is consistent with a diagnosis of TA: onset age <40 years, claudication of an extremity, decreased brachial artery pulse, >10 mm Hg difference in systolic blood pressure between arms, a bruit over the subclavian arteries or the aorta, and arteriographic evidence of narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper and lower extremities. Clinical classification of TA was defined in 4 subgroups as proposed by Lupi-Herrera et al and modified by us: (1) type I was presumed in patients with involvement of the aortic arch and its branches; (2) type II was confined to the ascending and descending aorta without involvement of the celiac artery and aortic arch; (3) type III was characterized by involvement of the descending aorta (from the end of aortic arch to the femoral artery); and (4) type IV was presumed in patients with involvement of all the aorta, its branches, and pulmonary arteries.
The following vascular risk factors were recorded: age, sex, hypertension, diabetes mellitus, hypercholesterolemia, cigarette smoking, ischemic heart disease, atrial fibrillation, and cardiac valve prosthesis. Noninvasive investigations including extracranial and TCD sonography as well as duplex sonography, 12-lead ECG, and transthoracic/transesophageal echocardiography were performed in all cases. Cerebral CT and MRI (T1-weighted, T2-weighted, and proton density–weighted images) were performed in patients with neurological involvement. Digital subtraction angiography by the Seldinger technique with the ascendant arch, descendant aorta, and subclavian and carotid arteries was performed in all patients. Spouses and psychiatric outpatients (100 subjects) in sinus rhythm without a history of vascular disease, claudication of extremities, decreased brachial artery pulse, or bruit over the aorta or carotid arteries were enrolled in the present study as a normal control group. All control subjects were evaluated by carotid duplex ultrasound to exclude a significant carotid stenosis (>50% diameter).

**Embolic Signal Monitoring**

Bilateral TCD ultrasonography monitoring was performed over the middle cerebral arteries (MCAs) by using 2-MHz probes of a pulsed Doppler machine (Multi-Dop X-4, DWL, with multirange embolus detection software TCD-8 for MDX, version 8.00K) for 30 minutes per patient and control subject. Both MCAs were simultaneously monitored through the temporal window at an insonation depth of 50 to 55 mm. In multigate Doppler ultrasonography evaluations, 2 different depths of the same vessel were monitored, and an intergate distance of 5 mm was used. The sweep time was ~6 seconds, and a velocity scale between ~100 and 150 cm/s was used. We used a 128-point fast Fourier transform resolution and set the high-pass filter at 100 Hz. Power was 160 mW/cm², and the pulse repetition frequency was 6500 Hz. A detection threshold of ≥9 dB was used to identify the microembolic events. Two examiners were present throughout the study and evaluated the monitoring results of the MCA online. The determination and detection of microemboli were performed according to the criteria of the International Consensus Group on Microembolus Detection: (1) characteristic acoustic properties, (2) short duration (<0.3 seconds), (3) random appearance in the cardiac cycle, (4) unidirectional signal, and (5) intensity increase at least 9 dB above the background. Differentiation of MES from artifacts was based on the criteria of consensus conference. Artifacts were assumed if signals were registered simultaneously on both sides or bidirectionally above and below the baseline. All data were stored on the hard disk for subsequent analysis. The examiners were blind to the status of all subjects, and they evaluated MES counts in the MCA independent from each other and were asked to note both the exact position of each MES on the recording and the total MES counts. The MES recordings were repeated twice to assess
interobserver agreement at the same point in time by 2 observers. Only signals recognized by both observers in 2 successive recordings were accepted as embolic in nature. Embolic signals were considered on the basis of the intensity and mean number of 2 consecutive recordings.

**Data Analysis**

The data were evaluated by using SPSS for Windows, release 8.0 (SPSS, Inc). Descriptive statistics were computed for each of the variables included in the present study. For between-group comparisons of continuous variables, $t$ tests were used. Significance was set at the $P<0.05$ level.

**Results**

There were 18 patients with TA (13 females and 5 males; mean age 37.4±14 years, range 17 to 62 years). The clinical time from the onset of symptoms was 1 to 11 years (mean 5.2±3.9 years) in patients. The topography of arterial lesions is demonstrated in the Figure. Twelve patients (67%) had type I arteritis, 1 (6%) had type II, 3 (17%) had type III, and 2 (11%) had type IV. Among atherosclerotic vascular risk factors, smoking was present in 6 (33%) patients, and hypertension, diabetes mellitus, and hypercholesterolemia were present in 1 (6%) patient for each. Other clinical manifestations were presented in the Table. Eight patients had ischemic stroke in the anterior circulation (6 patients) and posterior circulation (2 patients). The patients experienced ischemic stroke 6 months to 2 years (median 11 months) before the TCD ultrasonography recording. MES were present in 7 patients (22%), and the intensity of MES varied between 9 and 30 dB. None of the control subjects had MES. Patients with MES had type I (patients 5 and 18) and type III (patients 4 and 15) arteritis, and in 3 patients, MES were bilateral. Two patients with infarcts in the territory of the MCA showed MES. None of the patients with posterior cerebral artery territory infarction had MES, nor did the normal control group. The erythrocyte sedimentation rate (ESR) was higher in 10 patients during TCD ultrasonography monitoring, and 3 (30%) of them had MES. MES were found in 13% of the patients (1 of 8) with normal ESR. There was no significant statistical difference between these ESR groups ($P>0.05$). As an immunosuppressive therapy, 11 patients...
received methylprednisolone (16 mg/d), and 5 patients were treated with methotrexate (5 mg/wk) for a mean period of 3 years (range, 1 to 5 years). Warfarin was used in 5 patients (mean of international normalized ratio was 2.6) for 1.5 years (range 2 to 36 months), and aspirin (300 mg) was used in 6 patients for 1.8 years (range 1 to 4 years). There were no statistically significant differences for the methylprednisolone, methotrexate, warfarin, and aspirin treatment groups compared with the patients without treatment ($P > 0.05$). However, in 2 (67%) of the 3 patients who did not receive any treatment, the frequency of MES was higher than in those who received immunosuppressive therapy as a whole group (2 [18%] of 11 patients) before the TCD ultrasonographic monitoring ($P < 0.05$). The mean follow-up period was 2.1 months after MES recording, and during this period, we did not observe any recurrent stroke.

**Discussion**

TA can affect almost all large- and medium-sized arteries throughout the body. The neurological findings may develop because of either arterial hypertension or ischemic stroke. In type I and type IV arteritis, the carotid, subclavian, and brachiocephalic arteries are commonly narrowed and occluded. In approximately half the patients with TA, neurological manifestations are often transient and are focal or nonfocal in nature.3,8,9 In earlier literature, transient ischemic symptoms were thought to result from hypersensitivity of a carotid sinus or from a subclavian-steal phenomenon.10 Doppler flow studies show that brain stem ischemic symptoms seldom occur as consequences of a subclavian-steal phenomenon, probably because of well-maintained function in the circle of Willis.11,12 The findings from positron emission tomographic studies indicate that transient nonfocal ischemic symptoms can occur after reduction of cerebral perfusion pressure by hemodynamic mechanisms,13 although this mechanism could not explain multiple arterial territory/cortical-subcortical area infarction in TA. In the present study, nearly half of the patients had cerebral infarction; among them, two thirds had infarction in the superficial territory of the middle or posterior cerebral artery. In addition, digital subtraction angiography did not show any distal branch obstruction at the time of visualization, suggesting embolic mechanisms as a cause of these infarctions. We found that one fourth of the patients with ischemic stroke presented MES during TCD ultrasonography monitoring, suggesting an embolic mechanism in the pathogenesis of cerebral ischemia in TA.

In patients with TA, the inflammation primarily affects the aorta and extends into the cluster of arterial branches adjacent to primary lesion. Most commonly, the proximal portion of a vessel is affected, with continuation of the pathological process into the more distal portion. During the acute phase, inflammatory infiltrates usually consist of lymphocytes, plasma cells, and giant cells and involve all layers of the arterial wall. Thrombi are frequently observed distal to the sites of inflammatory changes. At the chronic phase, fibrous tissue replaces the damaged intima, media, and adventitia. Stenotic lesions develop and may resemble arteriosclerotic plaques.14–16 Our findings suggest that MES frequency was higher during the active phase of the disease, which was followed by ESR assessment, than during the silent chronic phase. The mechanism of the presence of MES in patients with type III arteritis could be explained by the generalized inflammatory changes through the aorta during the acute phase.

Angiography and ultrasonographic methods show luminal morphology but provide no information on the inflammatory status of the vessel wall in patients with TA.2,3,17–19 Thus, the finding of a patent vessel does not exclude the presence of early inflammation and active disease. A review of 33 surgical specimens demonstrated active inflammation in 20% of TA patients, and chronic changes of uncertain significance in 20%.20 Active focal skin lesions are often interspersed by inactive healed lesions and may contribute to the development of an embolus in the cerebrum. In the present study, 1 patient with stroke who had normal ESR exhibited MES, suggesting that an active inflammatory process in TA could continue in spite of a normal ESR and cause cerebral ischemia by embolic materials.

In TA patients, MES were present in more than two thirds of the patients who did not receive immunosuppressive therapy, whereas only one fifth of those who received treatment had MES, suggesting positive anti-inflammatory effects of these drugs on the vasculature, especially in the active phase.2,21

In conclusion, cerebral microembolus detection can be used as an additional noninvasive procedure in patients with TA during the acute and chronic phase of the disease. The monitoring of MES seems useful for selecting better treatment for long-term prophylaxis of disease from acute and recurrent stroke, but further large studies are required to justify the efficacy of immunosuppressive treatment in these patients.

**References**

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